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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,333	12/03/2001	Kathleen D. Danenberg	11220/146	5598

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,333	DANENBERG, KATHLEEN D.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,17,20 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,17,20 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/13/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action responds the Amendment received on November 12, 2004.

Preliminary Remark

Claims 1, 5, 17, 20, and 24-27 are pending and are under prosecution.

Applicants are advised that the limitation of multiple dependent claim 26 (multiple dependence on claims 20 and 25), regarding the mRNA being isolated in the presence of an effective amount of chaotropic agent is already present in claim 20, hence redundant[1].

Specification – Incorporation by Reference

The objection to the specification for containing the phrase, "incorporated by reference" pertaining to application 09/988,784, made in the Office Action mailed on August 11, 2004 is maintained for the reasons of record.

Applicants' arguments received on November 12, 2004 have been fully considered but they are not found persuasive.

As previously stated, incorporation by reference **must** be filed at the time the application is filed as Amendment cannot introduce new matter under 35 U.S.C. 132(a)[2].

The instant specification has been amended to incorporate by reference, U.S. Application Serial Number 09/988,784, in the Amendment received on October 24, 2003.

However, the Application as filed did not contain ***any*** reference to this application.

While Applicants argue that on page 13, 15, 23, and 24 of the specification contain reference to the application to which Applicants are attempting to incorporate by reference, U.S. Application serial number 09/988,784 was found nowhere in the specification. It appears that

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[1] Claim 26 is dependent on claim 20, which is further dependent on claim 17, which recites this limitation.

Applicants have amended page 13 in the instant Amendment received on November 12, 2004 to include this U.S. Application.

This is again improper because incorporation by reference can only be done at the time the application is filed, either in transmittal letter-as-filed, or an amendment specifically referred to in an oath or declaration executing the application.

Therefore, the instant amendment to the specification is denied for containing New Matter by way of including the phrase, "incorporation by reference" referring to U.S. Application 09/988,784.

Correction ***is*** required.

Priority

Applicants are advised that Applicants' claims to priority to the provisional application, 60/250,120 and 60/250,472 are **NOT GRANTED**.

The provisional application 60/250,120 (hereto referred to as the '120 application) and 60/250,472 (hereto referred to as the '472 application) do not contain proper written support under 35 U.S.C. 112, first paragraph, for the instantly claimed subject matter which pertains to the determination of metastatic cancer based on the detection of EGFR level.

The '120 application and the '472 application only contain written support for determining expression level of TS, which is thymidine synthase.

Hence the effective filing date for the instant application has been determined to be ***June 11, 2001.***

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[2] Page 3, 1st paragraph of the Office Action mailed on August 11, 2004.

Information Disclosure Statement

Applicants are advised that the IDS received on January 13, 2005 is acknowledged.

Applicants' statement regarding the references being cited in the PCT search report[3], under 37 CFR 1.704(d), however, is not entirely correct.

37 CFR 1.704 states:

> "A paper containing only an information disclosure statement in compliance with §§ 1.97 and 1.98 will not be considered a failure to engage in reasonable efforts to conclude prosecution (processing or examination) of the application under paragraphs (c)(6), (c)(8), (c)(9), or (c)(10) of this section if it is accompanied by a statement that each item of information contained in the information disclosure statement was first cited in any communication ***from a foreign patent office*** in a counterpart application and that this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement. This thirty-day period is not extendable."

The references cited in the IPER was generated from a U.S. Patent Office, and ***not*** from a foreign patent office.

Additionally, according to MPEP 609, a statement under 37 CFR 1.97(e) can contain ***either of two statements***:

a) One statement is that ***each*** item of information in an information disclosure statement was first cited in any communication, such as ***search report, from a patent office outside the U.S. in a counterpart foreign application not more than 3 months prior to the filing date of the statement.***

b) In the alternative, a statement can be made if ***no item*** of information contained in the information disclosure statement ***was cited in a communication from a foreign patent office*** and, to the knowledge of the person signing the statement after making reasonable inquiry,

neither it was known to any individuals having a duty to disclose more than 3 months prior to the filing of the statement.

Applicants satisfied neither of the two criteria under 37 CFR 1.97(e), and therefore, a fee under 37 CFR 1.17(p) has been charged.

A signed copy of the PTO-1449 is attached hereto.

Claim Rejections - 35 USC § 112

The rejection of claims 1, 5, 6, 17-20, and 24-27 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on August 11, 2004 is withdrawn in view of the claim amendment made in the Amendment received on November 12, 2004. With regard to the rejection of claims 1, 5, 6, 17-20, and 24-27 for being indefinite surrounding the term, "predetermined threshold," Applicants' traversal made on page 8 of the Response is found persuasive and therefore, withdrawn.

New Grounds – Necessitated by Amendment

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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[3] Page 2 of the IDS statement received on January 13, 2005.

Claims 1 and 5 recite the term, "mRNA levels of the EGFR tumor gene determinant." It is unclear what structure is encompassed by an mRNA level of an EGFR ***tumor gene determinant***. While one of ordinary skill in the art would readily recognize what structure encompassed by an mRNA level of an EGFR gene, one of ordinary skill in the art would not recognize what metes and bounds embraced by an mRNA of an EGFR tumor gene determinant as the mRNA is not from EGFR gene but from EGFR ***tumor gene determinant***.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5 , 17, 20, and 24-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

(A) Quantity of experimentation necessary: The quantity of experimentation necessary to practice the claimed method would require undue experimentation because the specification is

silent as to whether the expression levels of EGFR mRNA found is primary tumor samples are also indicative the metastatic tumor.

(B) Amount of guidance presented: The specification sets forth the importance of determining the ***degree of variation of gene expression between primary tumors and metastases***, and further states that there has been no reliable way of determining whether a particular chemotherapy directed toward the expression of a tumor gene determinant appropriate for a primary tumor ***is also*** appropriate for treating metasis (page 8, lines 11-18), stating that a significant association between levels of tumor determinant gene expression in primary tumor with expression of the same tumor determinant gene in ***matching metases acrchival samples***. (page 10, lines 8-10).

The specification gives guidance so far as to guide a skilled artisan to conduct a real-time amplification of EGFR gene via use of specific primer sets (SEQ ID NO: 1 and 2) and a TaqMan™ probe of SEQ ID NO: 3 (page 37, lines 4-6) and the normalization of the EGFR expressed via use of internal control such as β-actin (page 36, lines 1-3).

While the specification gives detailed information regarding the correlation between tumor gene determinant, TS (thymidylate synthase) expression in Primary and Metastases (beginning at page 48, line 20), specifically giving the mean expression values:

Source	Expression Level[4]
Primary Tumors	5.16×10^{-3}
Metastatic Tumors	4.5×10^{-3}

[4] Values from page 49, lines 6 and 7.

The specification even goes as far as giving the correlation coefficient (R^2) between TS expression values in the sets of primary and metastatic tissue, 0.95 (page 49, line 10).

The specification further states that there was a significan linear correlation between TS mRNA expression in the primary and secondary tumors (page 49, lines 17-23; Figure 1).

The specification, however, is **absolutely** silent on whether there were any correlation between the **claimed** tumor gene determinant, EGFR expression in Primary and Metastases. No expression levels whatsoever are given for EGFR for both the samples from primary and metastatic tumors. At best, the specification provides Figure 2, which illustrates how to calculate EGFR expression relative to internal control gene, which would guide a skilled artisan to calculate the expression level of EGFR in a sample. But the specification completely lacks evidence nor guidance for one skilled in the art to know that there were any correlation between primary and metastatic tumors expression EGFR.

(C) Absence of working example: The specification does not have any example for one skilled in the art to recognize that Applicants established any correlation for EGFR between primary and metastatic tumor.

(D) Nature of the Invention: The nature of the invention is drawn to detecting the level of EGFR expression in a primary tumor sample, and determining a chemotherapeutic regimen for treating a ***metastatic*** tumor based on the amount of EGFR mRNA in the primary tumor sample, ***wherein the correlation between the expression of EGFR in primary tumor and metastatic tumor had to have been established***.

The specification lacks this correlation.

(E) State of prior art: The ways in which an mRNA expression is measured for a particular gene are well-known. Techniques such as TaqMan™ assay (involving real-time PCR), as represented by U.S. Patent No. 5,952,202 (Aoyagi et al.); GeneChip™ from Affymetrix™, as represented by U.S. Patent no. 6,033,860 (Lockhart et al.) demonstrate the state of prior art.

(F) Skill level: The skill level of the practitioner is considered high.

(G) Unpredictability: Absent empirical determination, whether there exists a correlation for a particular marker between a primary and metastatic tumor exists, is unpredictable. Absent evidence to the contrary, such correlation would not exist,

One of skill in the art would first look to the specification for guidance in determining whether there exists some correlation between a primary and metastatic tumor for EGFR, to which none would be found. Other than the marker TS, one of skill in the art would not find such correlations, requiring the one of skill in the art to conduct undue experimentation to practice the claimed method because the claims require that such correlation exists for EGFR.

For the above reasons, the invention as claimed is not enabled.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot

guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
2/16/05

YOUNG J. KIM
PATENT EXAMINER

yjk